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REMARKS

Status of Claims

Claims 1-65 are pending in the application. Claims 3-5, 7, 9, 19, 21, 32-38, 40-42, 44, 49-62, 64 and 65 stand withdrawn from consideration. Claims 1, 2, 6, 8, 10-18, 20, 22-31, 39, 43, 45-48 and 63 were examined on the merits and stand rejected. Claim 39 has been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of claim 39 in this or future continuation/divisional application(s). Claim 1 has been amended to recite that the sulfated polysaccharide is “capable of binding to a protein.” Claims 1, 2 and 63 have been amended to recite that “said method is enzymatic only.” The dependency of claim 45 has been amended. New claims 66-71 have been added. Support for the amendments and new claim can be found throughout the specification, for example, at paragraphs [0010], [0015] and [0053], and in Figure 20. No new matter has been added.

CLAIM REJECTIONS

Double Patenting Rejections

Claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 stand provisionally rejected for obviousness-type double patenting over claims 13, 18, 19, 24, 29 and 30 of copending Application No. 11/204,391. Applicants respectfully disagree.

Applicants request that the provisional obviousness-type double patenting rejection be held in abeyance until allowable subject matter has been identified, at which time Applicants will consider filing a Terminal Disclaimer.

Claims 1, 2, 6, 8, 10-18, 20 and 22-31 stand provisionally rejected for obviousness-type double patenting over claims 1, 6, 16, 17, 19, 20, 23, 29, 39, 41, 42, 81, 85 and 88 of copending Application No. 10/986,058. Applicants respectfully disagree.

Applicants request that the provisional obviousness-type double patenting rejection be held in abeyance until allowable subject matter has been identified, at which time Applicants will consider filing a Terminal Disclaimer.

Rejections Under 35 U.S.C. § 112

Claim 39 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner asserts that it is unclear whether bonds that are not attached to another atom in the structures of polysaccharides 1, 10 and 11 indicate that the structure is repeated, or whether an atom was not drawn.

Applicants respectfully disagree. In order to further prosecution, however, claim 39 has been canceled, rendering the rejection moot.

New claim 66 has been added, directed to the synthesis of polysaccharide 15 from polysaccharide 11, via polysaccharides 12, 13 and 14.

As Applicants previously noted, after the use of e.g. heparitinase I (the synthesis of polysaccharide 11 from polysaccharide 10 in Figure 20), polysaccharide 11 becomes a discrete *hexasaccharide*, lacking the linking bonds at each end of the 6-unit repeating structure. Thus, polysaccharides 11, 12 and 13 are discreet *hexasaccharides*, lacking the linking bonds at each end of the 6-unit repeating structure.

Reaction of hexasaccharide 13 with, e.g., $\Delta^{4,5}$ -glycuronidase results in formation of a discrete *pentasaccharide*, 14. Thus, polysaccharides 14 and 15 are discreet *pentasaccharides*, also lacking the linking bonds at each end of the 5-unit repeating structure

Thus, each polysaccharide structure recited in claim 66 is definite. Accordingly, Applicants assert that claim 66 fully complies with the requirements of 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102

(i) Claims 1, 2, 8, 10 and 13-17 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Pikas, *Trends in Glycoscience and Glycotechnology*, 11, 61, 303-308, 1999 (“Pikas”). Applicants respectfully disagree.

Claims 1 and 2 have been amended to recite that the method described therein are *enzymatic* only. In contrast, Pikas discloses a method that involves a *chemical* N-deacetylation, a *chemical* and N-sulfation and a *chemical* O-sulfation. Indeed, the Examiner acknowledges that “the teachings of Pikas differ from the instantly claimed invention in that

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O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.”
See Final Office Action at page 8.

Accordingly, *Pikas* does not teach or suggest each and every element of the present claims and thus does not anticipate the present claims. Applicants respectfully request that the rejection be withdrawn.

(ii) Claims 1, 2, 6-10 and 13-17 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Wei *et al.*, *Proc. Natl. Acad. Sci.*, 90, 3885-3888, May 1993 (“Wei”). The Examiner asserts that the product of Wei is capable of binding to GlcA C5-epimerase, which is deemed to meet the limitations of a “binding partner.” Applicants respectfully disagree.

Claim 1 has been amended to recite that the sulfated polysaccharide is capable of binding to a protein. Applicants maintain that Wei does not teach, disclose or suggest a sulfated polysaccharide capable of binding to a protein.” Wei only teaches one step in the sulfation of a polysaccharide, the N-deacetylation-N-sulfation of the N-position of the glycosidic residue. The resulting incompletely sulfated polysaccharide is unable to bind to proteins known in the art. Wei recites “[h]eparan sulfate is a highly sulfated carbohydrate polymer that binds to....numerous proteins. The formation of these protein-binding domains in heparan sulfate is dependent on a series of biosynthetic reactions that modify the polysaccharide backbone; the initiating and rate limiting steps of this process are the N-deacetylation and N-sulfation of N-acetylglucosamine residues in the polymer.” *See* Wei Abstract (emphasis added).

Accordingly, Wei does not teach, disclose or suggest each and every element of the present claims and thus does not anticipate the present claims. Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

(i) Claims 6, 11, 12, 18, 20, 22-31, 46 and 47 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over *Pikas* in view of Esko *et al.*, *J. Clin. Invest.*, 108, 2, 169-173, 2001 (“Esko”). Applicants respectfully disagree.

Applicants assert that as discussed above, *Pikas* describes a process that involves several chemical steps (namely chemical N-deacetylation, N-sulfation and O-sulfation). Such

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chemical process is different from the *enzymatic only* process which is the subject matter of the present claims. Indeed, as noted above, the Examiner acknowledges that “the teachings of Pikas differ from the instantly claimed invention in that O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.” *See* Final Office Action at page 8.

An obviousness rejection requires a teaching or suggestion by the relied upon prior art of all the elements of a claim. *See* M.P.E.P. § 2141. As noted above, Pikas does not teach, disclose or suggest each and every element of the present claims. Accordingly, Pikas does not render obvious any of claims 6, 11, 12, 18, 20, 22-31, 46 and 47. Esko does not cure the deficiencies of Pikas.

Esko does not teach, disclose or suggest any *in vitro*, enzymatic only method as required by the present claims. Indeed, Esko teaches away from the presently claimed methods, stating that “the fine structure of the [product] ultimately depends on the regulated expression and action of multiple glycosyltransferases, sulfotransferases, and an epimerase, which are arrayed in the lumen on the Golgi apparatus.” *See* Esko at page 170, right hand column, last paragraph (emphasis added). Moreover, Esko does not teach, disclose or suggest which specific enzymes may be important for use in the presently claimed methods in order to synthesize Applicants specially modified saccharides, such as herapan sulfate and heparin-like polysaccharides. Indeed, Esko states that “[t]he precise structures of the corresponding binding sites and their distribution in the HS chains are unknown.” Esko goes on to state that “[c]learly, a major effort in the field should aim at understanding the functional properties of the biosynthetic enzymes, as required to generate specific (and sometimes overlapping) binding sites in the HS chains.” *See* Esko at page 171, right hand column, second paragraph (emphasis added).

Accordingly, neither Pikas or Esko, nor their combination, teach or suggest every limitation of the present claims. Moreover, one of ordinary skill would have had no motivation to combine the process of Pikas that requires several chemical steps, with the process of Esko, and would have had no reasonable expectation of success for the presently claimed methods based on such combination.

The Examiner asserts that it would be obvious to combine Pikos and Esko because “it is well known ... that the use of enzymes results in a defined product as enzymes are

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generally substrate specific.” Further, the Examiner asserts that the use of enzymes “allows one to sulfate only specific sites … allowing one to have better control over the generated product.” *See* Office Action at page 9. However, the Examiner has provided no comments or arguments of any kind to substantiate these two blanket statements. Indeed, the Examiner appears to be using Applicants specification to make such statements in hindsight. One of ordinary skill would not necessarily understand that the presently claimed enzymatic only methods could be used to prepare a sulfated polysaccharide capable of binding to a protein. As discussed at paragraph [0008] of the subject specification, previously known chemical methods for the synthesis of heparin sulfate suffer from numerous drawbacks including a very large number of synthetic steps, and the need for numerous protection and deprotection steps. In contrast, Applicants have developed rapid, convenient, sensitive and inexpensive enzymatic only methods for synthesizing specially modified saccharides, such as herapan sulfate and heparin-like polysaccharides that bind to proteins.

Since Pikas and Esko, when taken alone or in combination, fail to teach, suggest or disclose all the elements of the present claims, the Examiner has failed to establish a *prima facie* showing that the claims are obvious over a combination of Pikas and Esko. Accordingly, Applicants request withdrawal of the rejection.

(ii) Claims 39, 43, 45, 48 and 63 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Pikas in view of Kusche (PTO-892, page 2, Ref. U, “Kusche”), further in view of Habuchi *et al.*, *Trends in Glycoscience and Glycotechnology*, 10, 52, 65-80, 1998 (“Habuchi”), Nader *et al.*, *Glycoconjugate Journal*, 16:265-270, 1999 (“Nader”) and Myette *et al.*, *Biochemistry*, 41, 7424-7434, 2002 (“Mayette”). Applicants respectfully disagree.

Firstly, Applicants maintain, as discussed above, that Pikas does not teach, disclose or suggest any *in vitro*, enzymatic only method as required by the present claims. Further, the Examiner acknowledges that Pikas “does not teach the synthesis of pentasaccharide (15) from the *E. coli* polysaccharide using the instantly claimed method.” *See* Office Action at page 10.

An obviousness rejection requires a teaching or suggestion by the relied upon prior art of all the elements of a claim. *See* M.P.E.P. § 2141. Accordingly, Pikas fails to teach, suggest or disclose all the elements of the presently amended claims, and thus does not render obvious any of claims 39, 43, 45, 48 and 63.

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Kusche, Habuchi, Nader and/or Mayette do not cure the deficiencies of Pikas noted above. For example, none of Kusche, Habuchi, Nader and/or Mayette teach, disclose or suggest any *in vitro*, enzymatic only method for synthesizing heparin sulfate or a sulfated polysaccharide capable of binding to a protein, as required by the present claims.

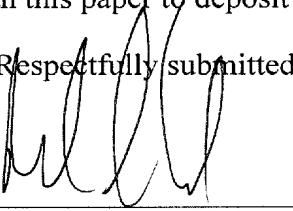
Since Pikas, Kusche, Habuchi, Nader and Mayette, when taken alone or in combination, fail to teach, suggest or disclose all the elements of the amended claims, the Examiner has failed to establish a *prima facie* showing that claims 39, 43, 45, 48 and 63 are obvious over a combination of these five references. Accordingly, Applicants request withdrawal of the rejection.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,



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Dated: December 23, 2009

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